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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/498,098	02/04/2000	Jeffrey Stack	AURO1330	8316

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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/498,098	Applicant(s) STACK ET AL.	
	Examiner J. Eric Angell	Art Unit 1635	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38,40,50,55,60 and 80-82* is/are pending in the application.

4a) Of the above claim(s) *55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-38,40,50,55,60 and 80-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Action is in response to the amendment filed 9/30/02 as Paper No. 15. Claim 39 has been cancelled. Claims 38, 40 and 50 have been amended. New claims 80-82 have been added. Claims 1-38, 40, 50, 55, 60 and 80-82 are pending in the application. Claim 55 has been withdrawn from consideration as being drawn to a non-elected invention for the reasons set forth in a previous Office Action. Claims 1-38, 50, 60 and 80-82 are examined herein.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action.
Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claim Rejections - 35 USC § 112, first paragraph

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-15, 17-28, 30-38, 40 and 60 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

1) A method of detecting an enzyme activity in a cell wherein the method comprises: providing a cell in vitro wherein said cell comprises a nucleic acid sequence encoding a protein, said protein comprising: steps 1a)-c) and 2) as set forth in claim 1 wherein detection of said reporter moiety or a product of said reporter moiety indicates detection of the activity in said cell;

2) A method of regulating the concentration of one or more target proteins in a cell in vitro, wherein said cell comprises a nucleic acid sequence encoding a protein, said protein comprising: steps 1a)-c) and 2) as set forth in claim 23;

3) A method of destabilizing a target protein in a cell in vitro, wherein said method comprises providing a cell in vitro, wherein said cell comprises a nucleic acid sequence encoding a polypeptide, wherein said polypeptide comprises a target protein operatively coupled to a linear multimerized destabilization domain, wherein said linear multimerized destabilization domain is non-cleavable by alpha-NH-ubiquitin protein endoproteases, and wherein said polypeptide comprises at least two copies of a destabilization domain, wherein said destabilization domain comprises a ubiquitin homolog; wherein said target protein is destabilized when expressed in said cell; and

4) An in vitro host cell comprising a nucleic acid sequence encoding a polypeptide, wherein said polypeptide comprises steps a)-c) as set forth in claim 60;

does not reasonably provide enablement for said methods and said cell wherein said methods and cell are in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims.

It is respectfully pointed out that the claims, as written, encompass both *in vitro* and *in vivo* embodiments. The in vivo embodiments of the claims embrace 1) methods of using transgenic animals engineered to express the chimeric destabilized polypeptide and 2) a transgenic cell expressing the chimeric polypeptide wherein said cell is in a transgenic animal (i.e. the cell is in vivo, in a transgenic animal).

The specification discloses how a cell can be engineered to express the chimeric destabilized polypeptide in vitro (e.g. by transducing a nucleic acid encoding the chimeric polypeptide into a cell in vitro; see Example 8, page 74 of the specification). Furthermore, the specification contemplates transgenic animals comprising a nucleic acid sequence encoding the chimeric polypeptide and methods of making and using the transgenic animals (see p. 8 of the specification). Therefore, the claims clearly encompass methods of using a transgenic animal which expresses said polypeptide and a transgenic cell in the transgenic animal (i.e. in vivo).

There is no evidence presented in the specification that any transgenic animal expressing the chimeric polypeptide in any cell has been successfully produced. Therefore, the embodiments of the claims encompassing an in vivo cell expressing said polypeptide and the in vivo methods are not enabled.

Although the claims are not explicitly drawn to methods of making and using transgenic animals or to the transgenic animals themselves (or cells thereof), the claims are not limited to exclude transgenic/in vivo embodiments. Looking to the specification for guidance, it is clear that the specification contemplates methods of making and using transgenic animals (see page 8 of the specification). Therefore, the claims are appropriately interpreted as encompassing transgenic animals (i.e. any transgenic animal) and methods of making/using the transgenic animals or cells thereof.

The state of the art at the time of filing regarding the production of transgenic animals was and continues to be unpredictable. For instance, it is well known in the art that the level and the specificity of expression of a transgene, as well as the phenotype of a transgenic animal, are greatly dependent on the specific transgene construct used. The individual gene of interest,

promoter, enhancer, coding, or non-coding sequences present in the transgene construct, the site of integration, etc. are all important factors in controlling the expression of the transgene. The art also recognizes problems with regard to producing animals of different species with identical phenotypes even when using a particular transgene to create both transgenic animals. For example, Wall (Theriogenology, Vol. 45, pages 57-68, 1996) teaches the unpredictability of transgene behavior due to factors such as position effect and unidentified control elements resulting in a lack of transgene expression or variable expression (paragraph bridging pages 61-62). Furthermore, Overbeek (Transgenic Animal Technology, pages 96-98, 1994) teaches that there can be considerable variation in the level of transgene expression in different transgenic animals (page 96, last paragraph). Therefore, it is recognized in the art that creating a particular phenotype in different transgenic animals is unpredictable.

In addition, the species-specific requirements for transgene design are not clearly understood. Examples in the literature aptly demonstrate that even closely related species carrying the same transgene construct can exhibit widely varying phenotypes. For example, several animal models of human diseases have relied on transgenic rats when the development of mouse models was not feasible. Mullins et al. (1990) produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse *Ren-2* renin transgene. Hammer et al. (1990) describe spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human β_2-microglobulin transgenes. Both investigations were preceded by the failure to develop similar phenotypes in transgenic mice expressing the same transgenes that successfully caused the desired symptoms in transgenic rats (see Mullins et al., 1989; and Taurog et al., 1988). Therefore, one of skill in the

art cannot readily predict that any transgenic animal will have the desired phenotype of interest without actually creating the transgenic animal.

The claims encompass methods of using transgenic animals expressing the chimeric polypeptide and cells of said transgenic animals. For instance, the claims encompass a method of detecting an activity in a cell *in vivo,* wherein said cell is a cell of a transgenic animal; a method of regulating the concentration of a target protein in a cell *in vivo,* wherein the cell is a cell of a transgenic animal; and a host cell expressing the chimeric protein wherein said cell is in a transgenic animal. The specification only discloses possible methods of creating non-human transgenic animals. The specification does not indicate that any transgenic animal expressing the polypeptide in any particular cell has been made. Due to the examples stated above which indicate that production of transgenic animals having a particular phenotype is unpredictable, one of skill in the art cannot readily predict that any transgenic animal expressing a transgene of interest in any particular cell can be produced.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above, the lack of direction and/or guidance in the specification, the absence of working examples for the making/using transgenic animals, the unpredictability of the art with respect to the expression of a transgene in any transgenic animal, and the breadth of the claims, it is concluded that an undue amount of experimentation is required for one skilled in the art to make and use the claimed invention with a reasonable expectation of success.

Response to Arguments

2. Applicant's arguments filed 9/30/02 have been fully considered but they are not persuasive.

3. It is asserted that it is Applicants' view that the claims are not directed to methods of producing transgenic organisms, or to transgenic organisms themselves, but to cells and methods of detecting activity in a cell, regulating protein expression in a cell, or a host cell itself. Applicants also contend that even if the cells are considered to be part of a transgenic organism, the factors that determine the success and operability of the claimed methods within the cell are defined and predictable, and as admitted in the Office Action, fully enabled by the present disclosure. Applicants also assert that factors which determine the ultimate phenotype of an adult transgenic animal are irrelevant because the claims are not directed to this feature as acknowledged on page 5, line 10 of the previous Office Action. Applicants point out that unexamined claims 64 and 68 are directed to transgenic organisms, and new claims 80-82 are directed to in vitro methods.

In response, as mentioned above, the claims encompass both *in vitro* and *in vivo* embodiments. Although the claims are not explicitly drawn to methods of making and using transgenic animals or to the transgenic animals themselves (or cells thereof), the claims are not limited to exclude transgenic/in vivo embodiments. Looking to the specification for guidance, it is clear that the specification contemplates methods of making and using transgenic animals (see page 8 of the specification). It is not inappropriate to interpret the claims as encompassing transgenic animals (i.e. any transgenic animal) and methods of making/using the transgenic animals or cells thereof, because the specification clearly contemplates such embodiments (see page 8). Furthermore, the claims are not fully enabled, but are only enabled for methods and cells that are in vitro only for the reasons stated above. Any statements in the previous Office Action indicating the claims are fully enabled were in error and are now withdrawn (this includes

the statement in the previous Office Action page 5, lines 9-12). Factors determining the ultimate phenotype of an adult transgenic animal are relevant because the claims encompass methods using transgenic animals expressing the chimeric protein and cells of said transgenic animal, furthermore the specification clearly contemplates such embodiments (see page 8 of the specification). It is pointed out that claims 64 and 68 were cancelled before any action was taken and are therefore irrelevant. It is also acknowledged that claims 80-82 are limited to in vitro embodiments are not considered included in this rejection (but are rejected under 35 USC 112, second paragraph, as indicated below).

Claim Rejections - 35 USC § 112, second paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-38, 40 and 80-82 rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The claims must include an indication that the cells comprise a nucleic acid encoding the chimeric polypeptide. The only guidance provided in the specification for a cell comprising the chimeric polypeptide indicates that the cell comprises a nucleic acid encoding and expressing the polypeptide (e.g., see Example 8 of the specification). Without a clear indication that the cell comprises said nucleic acid which encodes said polypeptide, it is unclear how the cell would comprise the chimeric polypeptide as no guidance or methods are provided in the specification.

6. Claims 1-22, 38, 40 and 60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Method claims require an active or positive step that accomplishes the goals for the method which were stated in the method's preamble. The instant claims lack such a step and are confusing because the additional method step(s) is not sufficiently set forth. While minute details are not required in method claims, at least the basic steps must be recited in a positive, active fashion. See Ex parte Erlich, 3 USPQ2d1011, p.1011 (Bd. Pat. App. Int. 1986).

The specific problem with claims 1-22 is that the steps presented are simply a method of detecting an activity in a cell. There is no requirement or active or positive step in the claims that activity is detected. This is indefinite because it leaves the scope of the claim unclear as to whether it is required that the activity be detected.

The specific problem with claims 38 and 40 is that the steps presented are simply a method of destabilizing a target protein in a cell. There is no requirement or active or positive step in the claims that the target protein is destabilized. This is indefinite because it leaves the scope of the claim unclear as to whether it is required that the protein be destabilized.

Claim 60 recites the phrase, "a nucleic acid sequence encoding for". This phrase renders the claim indefinite because it is unclear how a nucleic acid "encodes for" something. Amending the claim to recite, "a nucleic acid sequence encoding" would obviate this rejection.

Claim Objections

7. Claims 23, 38, 50 and 60 are objected to because of the following informalities: the claims recite the phrase "a NH-ubiquitin protein proteases" (see claim 23, lines 6 and 16; claim 38, lines 3-4; claim 50 lines 3-4 and 9-10; claim 60 lines 3-4 and 9-10). It is believed that the errors are only typographical errors. Appropriate correction is required.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

DAVE T. NGUYEN
PRIMARY EXAMINER

J. Eric Angell
December 14, 2002